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# Rosuvastatin Affecting Aortic Valve Endothelium to Slow the Progression of Aortic Stenosis

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**Objectives** The objective of this study was to test the effect of a 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor on the progression of moderate to severe aortic stenosis as measured by echocardiography.

**Background** Recent retrospective studies support the hypothesis that statins slow the progression of aortic stenosis.

**Methods** We performed an open-label, prospective study evaluating 121 consecutive patients with asymptomatic moderate to severe aortic stenosis (aortic valve area ≥ 1.0 $cm^2$; mean age 73.7 ± 8.9 years; 57 men and 64 women), treated with and without rosuvastatin according to the National Cholesterol Education Program Adult Treatment Panel III guidelines. Echocardiographic, serum lipid, and inflammatory markers were measured at baseline and every 6 months for 18 months.

**Results** Sixty-one patients (50.4%) with elevated LDL (159.7 ± 33.4 mg/dl), aortic valve velocity (3.65 ± 0.64 m/s), and aortic valve area (1.23 ± 0.42 $cm^2$) received rosuvastatin (20 mg/day), and 60 (49.6%) with a normal LDL (118.6 ± 37.4 mg/dl), aortic valve velocity (3.62 ± 0.61 m/s), and aortic valve area (1.20 ± 0.35 $cm^2$) received no statin. During a mean follow-up of 73 ± 24 weeks, the change in aortic valve area in the control group was −0.10 ± 0.09 $cm^2$/year versus −0.05 ± 0.12 $cm^2$/year in the rosuvastatin group ($p = 0.041$). The increase in aortic valve velocity was 0.24 ± 0.30 m/s/year in the control group and 0.04 ± 0.38 m/s/year in the rosuvastatin group ($p = 0.007$). There was significant improvement in serum lipid and echocardiographic measures of aortic stenosis in the statin group.

**Conclusions** Prospective treatment of aortic stenosis with rosuvastatin by targeting serum LDL slowed the hemodynamic progression of aortic stenosis. This is the first prospective study that shows a positive effect of statin therapy for this disease process. (Rosuvastatin Affecting Aortic Valve Endothelium; http://www.clinicaltrials.gov/ct/show/NCT00114491?order = 1; NCT0014491). (J Am Coll Cardiol 2007;49:554–61) © 2007 by the American College of Cardiology Foundation

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Calcific aortic stenosis is the most common indication for surgical valve replacement (1). The number of valve replacements is increasing because of the aging population (2). Currently, the only established therapy for patients with severe symptomatic aortic stenosis is surgical valve replacement (3,4). In 1997, Stewart et al. (5) defined the independent risk factors associated with calcific aortic stenosis from the Cardiovascular Health Study, which include: elevated lipoprotein (a), low-density lipoprotein (LDL) cholesterol, hypertension, male gender, and smoking. These risk factors are similar to the risk factors defined for coronary heart disease by the Framingham Heart Study, and have been validated in other aortic stenosis risk factor databases (6–10).

Until recently, the mechanism of degenerative aortic stenosis was thought to be caused by a passive accumulation of calcium along the surface of the aortic valve leaflet. However, there are a growing number of experimental studies showing that aortic valve calcification is an active biological process that can be targeted with medical therapy such as statins (11–13).

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Recently, this hypothesis has been confirmed with an increasing number of retrospective studies showing the effects of statins and angiotensin-converting enzyme inhibitors in slowing the progression of aortic valve stenosis (6,14–18).

We hypothesized that 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors may slow the

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hemodynamic progression of calcific aortic stenosis and improve inflammatory markers that have been described clinically to affect the aortic valve endothelium (19–21). To test this hypothesis we examined the effects of rosuvastatin in an open-label prospective study to determine whether an HMG CoA reductase inhibitor can slow the progression of moderate to severe aortic stenosis as defined by echocardiographic parameters (21–24). We treated a population of patients with elevated cholesterol levels and moderate to severe aortic stenosis and measured the hemodynamic progression by echocardiography (25). We also monitored serum LDL cholesterol in these patients to determine whether rosuvastatin can slow the progression of aortic stenosis using a targeted therapeutic approach.

**Abbreviations and Acronyms**

**ANOVA** = analysis of variance

**HMG CoA** = 3-hydroxy-3-methylglutaryl coenzyme A

**hsCRP** = high-sensitivity C-reactive protein

**IL** = interleukin

**LDL** = low-density lipoprotein

## Methods

We performed an open-label, prospective study on patients who have moderate to severe aortic stenosis as defined by an aortic valve area between 1.0 and 1.5 $cm^2$. We treated 121 patients presenting consecutively with asymptomatic aortic stenosis to the cardiology clinic in Hospital Pedro Hispano (age 73.7 ± 8.9 years; 57 men, 64 women) with and without rosuvastatin according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) guidelines. Patients with elevated LDL >130 mg/dl received rosuvastatin and those with LDL <130 mg/dl did not receive the therapy. Echocardiographic and serum markers for high-sensitivity C-reactive protein (hsCRP), interleukin (IL)-6, and CD40 were measured at baseline and every 6 months for 18 months. Table 1 shows the baseline clinical characteristics in of all the patients enrolled.

At study entry, the following clinical data were collected: age, gender, history of smoking, hypercholester-

**Table 1 Baseline Clinical Characteristics**

| Characteristic | All Patients (n = 121) | Statin-Treated Group (n = 61) | Untreated Group (n = 60) | p Value |
|---|---|---|---|---|
| Clinical | | | | |
| Age (yrs) | 73.7 ± 8.9 | 73.4 ± 8.5 | 73.9 ± 9.4 | 0.749 |
| Men, n (%) | 57 (47.1) | 21 (34.4) | 36 (60.0) | 0.006 |
| Arterial hypertension, n (%) | 77 (63.6) | 45 (73.8) | 32 (53.3) | 0.024 |
| Diabetes, n (%) | 39 (32.2) | 26 (42.6) | 13 (21.7) | 0.019 |
| Smokers, n (%) | 4 (3.3) | 0 (0) | 4 (6.7) | 0.057 |
| Sinus rhythm, n (%) | 106 (87.6) | 56 (91.8) | 50 (83.3) | 0.179 |
| Diastolic blood pressure (mm Hg) | 75.9 ± 12.9 | 78.4 ± 13.6 | 73.4 ± 13.6 | 0.033 |
| Systolic blood pressure (mm Hg) | 150.6 ± 22.9 | 154.4 ± 18.6 | 146.6 ± 26.2 | 0.060 |
| Cardiac frequency (beats/min) | 72.8 ± 13.0 | 73.8 ± 13.1 | 71.8 ± 12.8 | 0.379 |
| Laboratory analysis | | | | |
| Total cholesterol level (mg/dl) | 217.7 ± 50.1 | 243.0 ± 40.5 | 192.0 ± 45.8 | <0.001 |
| HDL (mg/dl) | 54.0 ± 12.7 | 55.0 ± 13.2 | 53.1 ± 12.2 | 0.399 |
| LDL (mg/dl) | 137.5 ± 39.6 | 158.2 ± 31.7 | 116.5 ± 20.9 | <0.001 |
| TG (mg/dl) | 133.6 ± 89.4 | 152.1 ± 102.3 | 114.5 ± 69.7 | 0.022 |
| SAA (mg/dl) | 0.6 (0.4–1.0) | 0.6 (0.3–0.8) | 0.7 (0.4–0.8) | 0.370 |
| IL-6 (pg/ml) | 12.7 (9.5–18.0) | 12.7 (9.4–18.0) | 12.5 (9.8–19.1) | 0.510 |
| TNF (pg/ml) | 10.3 (5.7–15.6) | 10.4 (7.0–13.4) | 9.2 (5.7–17.0) | 0.965 |
| BNP (pg/ml) | 40.0 (19.8–90.5) | 34.7 (15.5–83.4) | 47.0 (24.6–91.6) | 0.095 |
| hsCRP (mg/l) | 2.5 (1.0–6.7) | 2.7 (1.0–6.8) | 2.0 (1.0–5.1) | 0.477 |
| sCD40L (ng/ml) | 1.97 ± 1.07 | 2.05 ± 1.14 | 1.89 ± 0.99 | 0.414 |
| Echocardiographic | | | | |
| Peak jet velocity (m/s) | 3.63 ± 0.62 | 3.65 ± 0.64 | 3.62 ± 0.61 | 0.788 |
| Peak gradient (mm Hg) | 54.3 ± 18.5 | 54.7 ± 18.9 | 53.9 ± 18.2 | 0.828 |
| Mean gradient (mm Hg) | 35.7 ± 13.3 | 35.3 ± 13.4 | 36.1 ± 13.4 | 0.752 |
| Aortic valve area ($cm^2$) | 1.21 ± 0.38 | 1.23 ± 0.42 | 1.20 ± 0.35 | 0.636 |
| LV diastolic (mm) | 51.7 ± 5.1 | 50.1 ± 5.8 | 52.5 ± 4.1 | 0.110 |
| LV systolic (mm) | 33.9 ± 4.4 | 33.2 ± 4.9 | 34.6 ± 3.8 | 0.070 |
| EF (%) | 54.9 ± 3.1 | 54.3 ± 3.1 | 55.6 ± 4.4 | 0.060 |

Data are presented as mean ± SD when the variables are normally distributed and as mean (interquartile range) when non-Gaussian. Comparison groups were based on an analysis of variance (ANOVA) for variables with normal distribution or on a Mann-Whitney test for non-Gaussian variables. $p < 0.05$ for differences between groups.

BNP = brain natriuretic peptide; EF = ejection fraction; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; IL = interleukin; LDL = low-density lipoprotein; LV = left ventricular; SAA = serum amyloid A; sCD40L = soluble CD40 ligand; TG = triglycerides; TNF = tumor necrosis factor.

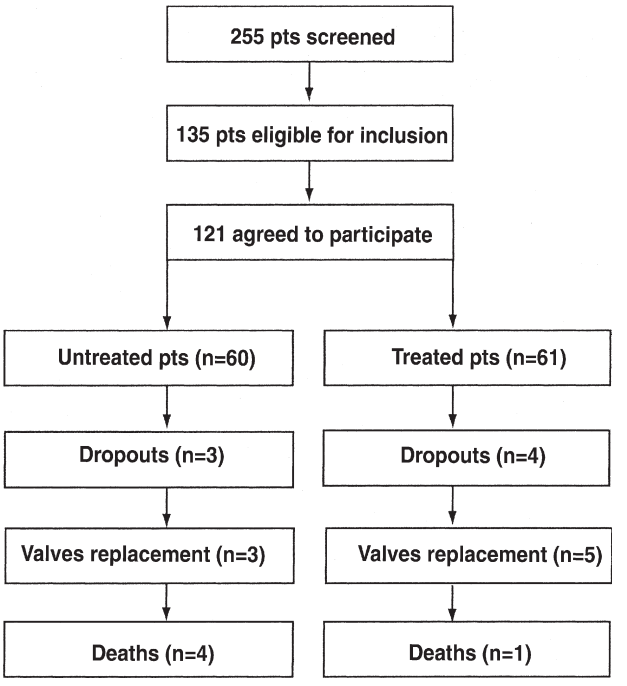


**Figure 1** Patient Flow Diagram

Flow chart of patient enrollment. pts = patients.

olemia, diabetes mellitus, arterial hypertension (blood pressure >140/90 mm Hg based on the average of repeated measurements), or coronary artery disease (documented previous myocardial infarction or angiographically documented coronary artery stenosis). There was no new initiation of statin therapy in the untreated group during the course of the study. No patients in the treatment group discontinued the statin treatment. Patients taking antihypertensive medications such as calcium antagonists, beta-blockers, and diuretics and as indicated on oral antidiabetics or insulin for diabetes were included in this study. Patients on angiotensin-converting enzyme inhibitors were excluded.

The 2 primary end points included progression of aortic stenosis and improvement in LDL cholesterol. Secondary end points were the improvement in the inflammatory markers. Patients excluded were those with coronary artery disease as measured by clinical history, echocardiographic evidence of rheumatic mitral valve disease, previous statin therapy, congenital heart disease (bicuspid aortic valve), subaortic obstruction, creatinine ≥2.0 mg/dl (to avoid the potential confounder of an elevated serum $CaPO_4$), active or chronic liver disease, mild aortic regurgitation, and previous aortic valve surgery. These subjects were asymptomatic as defined by clinical history, without clinical evidence of vascular, neoplastic, metabolic, or inflammatory disease by careful clinical history, examination, and routine laboratory tests. Institutional review board approval (IRB-22352) from Hospital Pedro Hispano was obtained before study initiation, and each study participant signed an informed consent before enrollment. Rosuvastatin (Crestor, Astra Zeneca, Wilmington, Delaware) was provided to the investigators without any intellectual or financial contribution from Astra Zeneca. Figure 1 shows the flow diagram from the initial time of patient screening to the composition of the final patient population. Trial registration was completed (Clinical Trials Government Identifier NCT0014491). Patients on antihypertensive medications such as calcium antagonists, beta-blockers, and diuretics and as indicated on oral antidiabetics or insulin for diabetes were included in this study. Patients on angiotensin-converting enzyme inhibitors were excluded. In the untreated group there was no initiation of the statin therapy. None of the patients on statin therapy developed any adverse reactions to the medication. There was 1 patient who developed symptoms and underwent aortic valve replacement. The cause of death in the statin-treated group was sudden death, and the family did not request an autopsy. In the nonstatin group the cause of death in 2 patients was sepsis, and 2 patients had a malignancy.

**Echocardiographic measurements.** Comprehensive transthoracic echocardiograms were performed in a single echocardiographic laboratory. Immediate physician review (level III) allowed re-imaging for quality control. Standard Doppler measurements of the left ventricular outflow tract and the aortic valve from multiple windows to obtain the

**Table 2** Changes in Hemodynamic Markers

| | Untreated Patients | | | Treated Patients | | |
|---|---|---|---|---|---|---|
| Characteristic | Baseline | Follow-Up | p Value | Baseline | Follow-Up | p Value |
| Peak jet velocity (m/s) | 3.56 ± 0.56 | 3.86 ± 0.62 | <0.001 | 3.64 ± 0.65 | 3.73 ± 0.74 | 0.112 |
| Peak gradient (mm Hg) | 52.1 ± 16.2 | 61.3 ± 19.4 | <0.001 | 54.3 ± 19.1 | 57.7 ± 22.3 | 0.072 |
| Mean gradient (mm Hg) | 34.7 ± 12.1 | 40.4 ± 14.7 | <0.001 | 34.9 ± 13.7 | 39.1 ± 16.6 | 0.004 |
| Aortic valve area ($cm^2$) | 1.24 ± 0.35 | 1.11 ± 0.35 | <0.001 | 1.22 ± 0.40 | 1.16 ± 0.42 | 0.010 |
| LV diastolic (mm) | 52.6 ± 4.2 | 53.9 ± 2.6 | 0.005 | 50.1 ± 7.1 | 53.7 ± 5.0 | <0.001 |
| LV systolic (mm) | 34.1 ± 4.0 | 35.7 ± 2.3 | 0.008 | 33.2 ± 5.3 | 35.1 ± 3.3 | 0.010 |
| EF (%) | 55.9 ± 4.7 | 57.9 ± 3.7 | 0.017 | 53.5 ± 3.6 | 58.0 ± 3.4 | <0.001 |

Data are presented as mean ± SD. Hemodynamic changes were assessed by paired *t* test. $p < 0.05$ for differences between baseline and follow-up data.

Abbreviations as in Table 1.

**Table 3** Annualized Changes in Hemodynamic Markers

| Characteristic | Untreated Patients | Treated Patients | p Value |
|---|---|---|---|
| Peak jet velocity (m/s/yr) | 0.24 ± 0.30 | 0.04 ± 0.38 | 0.007 |
| Aortic valve area ($cm^2$/yr) | −0.10 ± 0.09 | −0.05 ± 0.12 | 0.041 |
| Peak gradient (mm Hg/yr) | 7.57 ± 9.62 | 2.13 ± 12.91 | 0.010 |
| Mean gradient (mm Hg/yr) | 5.06 ± 7.17 | 2.08 ± 8.15 | 0.049 |

Data are presented as mean ± SD. Treatment comparisons for hemodynamic variables were based on analysis of covariance analysis. $p < 0.05$ for differences between groups.

maximum velocity were recorded, and the mean gradient, the peak velocity, and the aortic valve area were measured and calculated as defined by the American Heart Association/American College of Cardiology guidelines for the clinical application of echocardiography (26). For assessment of hemodynamic progression, echocardiographic studies were used. The data were obtained by 2 observers (L.M. and I.B.) who were blinded to the treatments. We reported the mean value between the 2 echocardiographic readers. Reproducibility of echocardiography was determined in a subset of 30 patients. Intraobserver and interobserver coefficients of reproducibility (27) were 0.22 $cm^2$ and 0.18 $cm^2$ for aortic valve area, and 0.22 m/s and 0.16 m/s for aortic valve peak velocity, respectively, between the 2 echocardiographic physicians (L.M. and I.B.).

**Inflammatory markers.** Patients fasted for 12 h and then serum was obtained at the time of randomization and at 6, 12, and 18 months of follow-up, and serum was immediately centrifuged at 1,000 *g* at 4°C for 20 min. Plasma was separated into aliquots and shipped to a central laboratory, where it was stored at −80°C for batch analysis.

**Laboratory tests.** We analyzed plasma IL-6 (Cell Com, Beckman Coulter, Nyon, Switzerland), and soluble CD40 ligand (sCD40L) (Biosource, Camarillo, California). The hsCRP (Dada Behring, New Castle, Delaware) levels were measured by a high-sensitivity assay. All assays have reported intra-assay and inter-assay coefficients of variation: <5% and <15%, respectively. In addition, lipid profiles, serum creatinine levels, glucose, aldolase, creatine phosphokinase, aspartate transaminase, and alanine transaminase were assessed by standard methods in our laboratories, and all values were within normal limits from standard laboratory values (data not shown).

**Statistical analysis.** Patient characteristics are presented as a number (percentage) for categorical variables, as mean ± SD when the variables are normally distributed or as median with interquartile ranges when non-Gaussian. To test the normality of continuous variables, we used the Kolmogorov-Smirnov test with Liliefors correction (parameters distribution unknown). Reproducibility was assessed by the method of Bland and Altman (27), and expressed as the coefficient of reproducibility (twice the SD of the differences). We used the criteria for a normally distributed population to decide between the tests. Analysis of variance (ANOVA) and the paired Student *t* test are parametric procedures used when the population is normally distributed. The Mann-Whitney *U* test and Wilcoxon tests are the nonparametric alternative tests for ANOVA and paired Student *t* test, respectively. Group comparisons for continuous outcome variables were analyzed using ANOVA or Mann-Whitney *U* test. Comparisons of follow-up data used paired Student *t* test or Wilcoxon test as appropriate. Chi-square tests were used to evaluate differences in the categorical variables. Aortic stenosis progression was determined by dividing the change between the final and baseline measurements by the duration of follow-up. Treatment comparisons for aortic stenosis progression variables were based on an analysis of covariance. The variables/covariates used were LDL cholesterol, age, hypertension, diabetes, baseline aortic valve area, baseline peak jet velocity, and baseline peak and mean gradients. The Pearson coefficient has been used to assess the linear correlation between the change in LDL cholesterol levels and aortic stenosis progression. Analyses were performed using SPSS software, version 12.0 (SPSS Inc., Chicago, Illinois). A two-tailed p value $< 0.05$ was considered to indicate statistical significance.

## Results

During a mean follow-up of 73 ± 24 weeks, the decrease in aortic valve area in the nonstatin group was −0.10 ± 0.09 $cm^2$/year versus −0.05 ± 0.12 $cm^2$/year in the statin treatment group ($p = 0.041$). The increase in peak aortic

**Table 4** Changes in Serum Markers

| | Untreated Patients | | | Treated Patients | | |
|---|---|---|---|---|---|---|
| Characteristic | Baseline | Follow-Up | p Value | Baseline | Follow-Up | p Value |
| Total cholesterol (mg/dl) | 193.7 ± 47.9 | 195.1 ± 37.1 | 0.830 | 245.5 ± 41.7 | 175.4 ± 31.6 | <0.001 |
| LDL cholesterol (mg/dl) | 118.6 ± 37.4 | 117.8 ± 29.2 | 0.882 | 159.7 ± 33.4 | 93.3 ± 21.1 | <0.001 |
| TG (mg/dl) | 116.2 ± 71.1 | 116.7 ± 60.0 | 0.945 | 153.9 ± 107.8 | 124.0 ± 57.8 | 0.003 |
| hsCRP (mg/l) | 2.4 (1.0–6.9) | 1.9 (0.8–4.9) | 0.363 | 2.7 (1.1–6.9) | 2.3 (0.9–5.1) | 0.030 |
| IL-6 (pg/ml) | 12.5 (9.8–19.1) | 2.9 (2.9–7.8) | <0.001 | 12.7 (9.4–18.0) | 2.9 (2.9–5.2) | <0.001 |
| sCD40L | 2.01 ± 0.97 | 0.93 ± 0.55 | <0.001 | 2.36 ± 1.04 | 1.06 ± 0.93 | <0.001 |

Data are presented as mean ± SD when the variables are normally distributed and as median (interquartile range) when non-Gaussian. Comparisons of follow-up data used a paired *t* test for variables with normal distribution or a Wilconxon test for non-normally distributed variables. $p < 0.05$ for differences between groups.

Abbreviations as in Table 1.

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valve velocity in the nonstatin group was +0.24 ± 0.30 m/s/year versus +0.04 ± 0.38 m/s/year (p = 0.007) in the statin group. The progression in peak gradient over the follow-up period for the nonstatin group was +7.57 ± 9.62 mm Hg/year, and was +2.13 ± 12.91 mm Hg/year (p = 0.010) in the statin group. The change in mean gradient was +5.06 ± 7.17 mm Hg/year in the nonstatin group versus +2.08 ± 8.15 mm Hg/year in the statin group (p = 0.049).

The primary end points in Table 2 show the numerical values for the hemodynamic parameters at baseline and at the end of the study. Table 3 shows the comparison of the annual changes in the hemodynamic measurements in the 2 groups with statistical improvement in the peak jet velocity, aortic valve area, peak gradient, and mean gradient. The secondary end points are shown in Table 4. The treated patients had improvement of all of the serum markers: total cholesterol, LDL cholesterol, triglycerides, hsCRP, IL-6 and sCD40L. Figure 2 shows the comparison data for the treated versus untreated groups at 0, 26, 52, and 78 weeks. Figures 2A, 2B, and 2C show the improvement in the peak jet velocity, mean gradient, and aortic valve area in the treated versus untreated population. Figures 3A, 3B, and 3C show a weak but statistically significant correlation of the improvement in peak jet velocity, mean gradient, and aortic valve area with the change in LDL cholesterol levels.

## Discussion

In the RAAVE (Rosuvastatin Affecting Aortic Valve Endothelium) study, we found a change in aortic valve area in the control group of −0.10 ± 0.09 $cm^2$ per year versus −0.05 ± 0.12 $cm^2$ per year in the rosuvastatin group (p = 0.041). In addition, the increase in peak aortic valve velocity was +0.24 ± 0.30 m/s/year in the control group as compared with +0.04 ± 0.38 m/s/year in the rosuvastatin group (p = 0.007). These data indicate that in this small prospective hypothesis-driven study we found a slowing of progression of aortic valve disease by echocardiography. Emerging epidemiologic and histologic studies have shown convincing clinical risk factor evidence toward an inflammatory atherosclerotic hypothesis for the cellular mechanism of aortic valve stenosis (5–9,28–31). Galante et al. (21) have shown a correlation with serum hsCRP levels, a serum inflammatory marker, with the severity of aortic valve stenosis. Furthermore, there are a growing number of in vivo experimental models showing that experimental hypercholesterolemia induces an atherosclerotic valve lesion that becomes stenotic (11). These stenotic valves express bone matrix markers and calcification markers that are attenuated with atorvastatin therapy (12,32,33). This clinical, epidemiologic, and experimental evidence suggests that aortic valve stenosis is an atherosclerotic process similar to vascular atherosclerosis. Currently, there are 6 retrospective studies that consistently show that statin therapy is associated with slowing of the hemodynamic progression of aortic stenosis (6,10,14–17). Therefore, targeting this disease with medical therapy may be an important therapeutic strategy in the future.

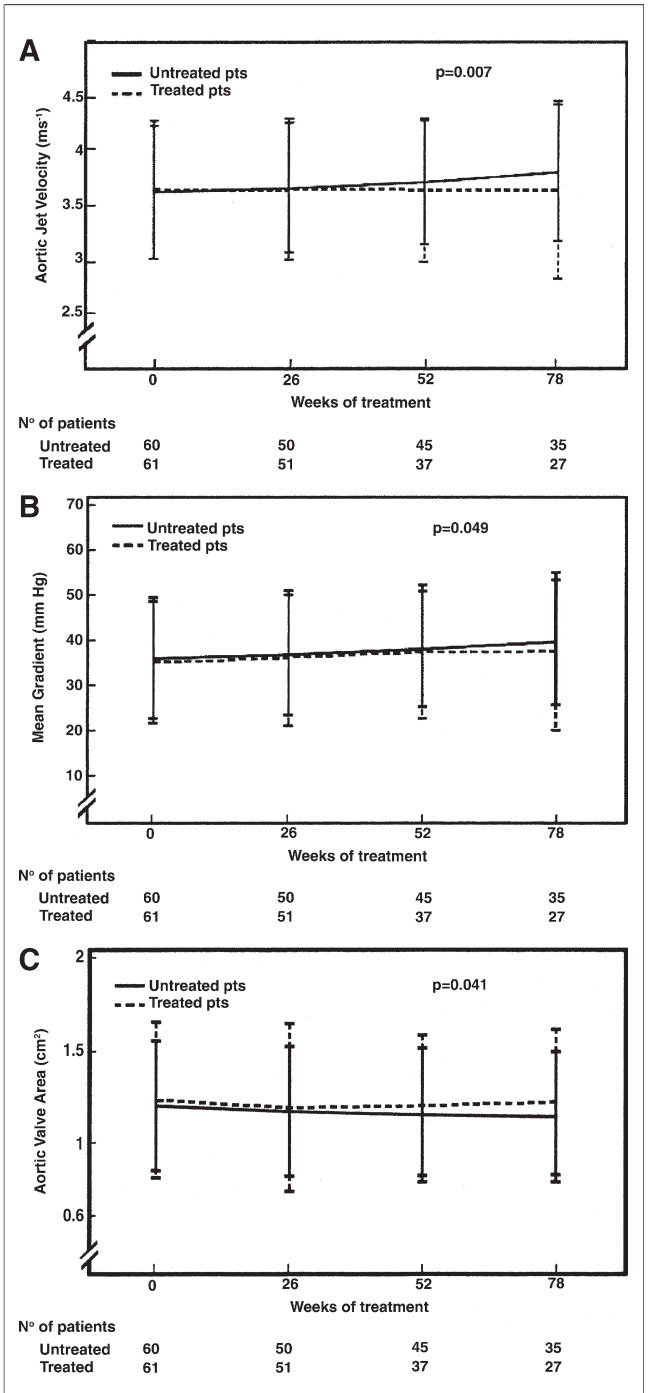


**Figure 2** Progression of Aortic Valve Stenosis in Patients Treated With Rosuvastatin Therapy and Untreated Patients

**(A)** Aortic jet velocity in treated versus untreated patients. **(B)** Aortic mean gradient in treated versus untreated patients. **(C)** Aortic valve area in treated versus untreated patients.

In the RAAVE study, we treated patients who presented with asymptomatic aortic stenosis and elevated cholesterol levels as defined by the NCEP-ATPIII guidelines. This study shows that statins slow the primary end points of hemodynamic progression as measured by peak velocity, aortic valve area, peak gradient, and mean gradient. Sec-

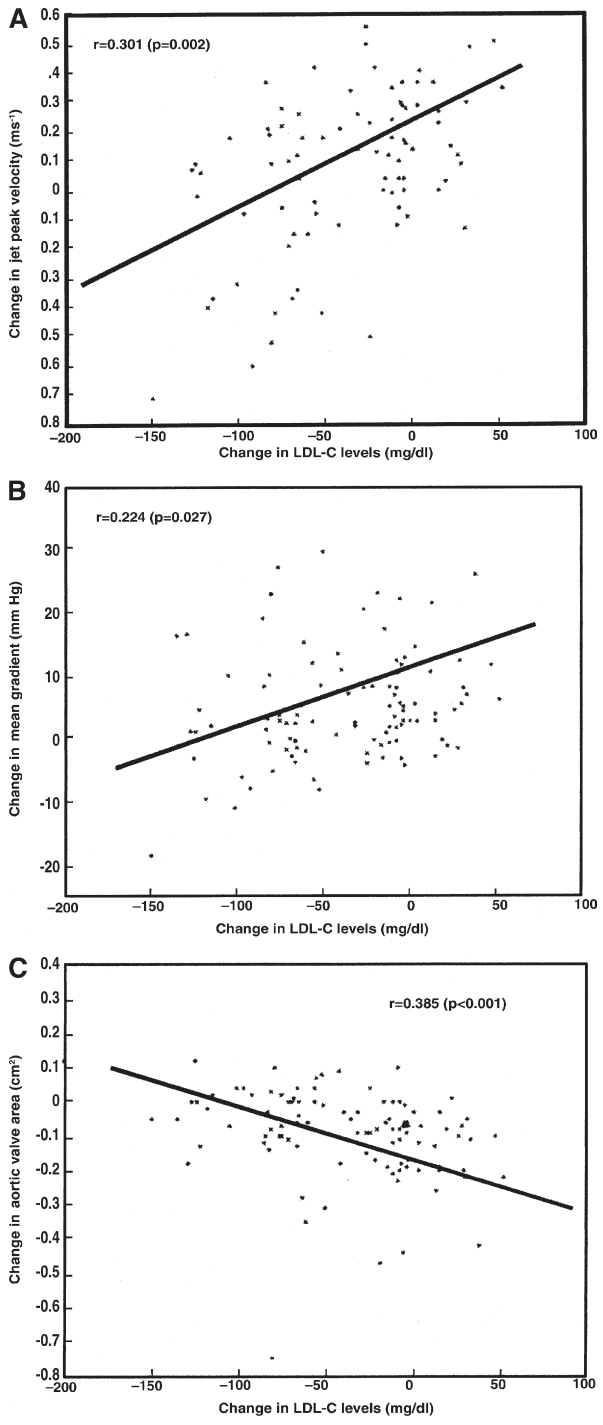


**Figure 3** **Correlation of LDL Cholesterol With Echocardiographic Hemodynamic Measurements in Treated Patients**

**(A)** Aortic jet velocity in treated patients. **(B)** Aortic mean gradient in treated patients. **(C)** Aortic valve area in treated patients. LDL = low-density lipoprotein.

ondary end points including CRP levels, IL-6, sCD40L, and serum LDL levels were all reduced significantly in the rosuvastatin-treated patients with moderate aortic stenosis. The RAAVE study confirms the data from Otto et al. (34), which indicate that the rate of hemodynamic progression in a prospective study of asymptomatic aortic stenosis can be measured specifically by the rate of change in jet velocity ($p < 0.001$). Our data also indicate that the patients in the untreated group with a lower risk factor profile in terms of serum LDL have a lower inflammatory profile over the follow-up period. We hypothesize that if the biology of the aortic valve is a bone differentiation process as described by Mohler et al. (35), and Rajamannan et al. (36), then as more bone forms and the valve calcifies there may be a decrease in the inflammatory states that are present in the earlier aortic valve lesion (37). A recent study by Sanchez et al. (38) has also shown lower levels of CRP in patients who had a slower rate of progression. These inflammatory marker data are only observations and do not provide any confirmative direct evidence of the biological disease activity in these patients.

The first prospective study testing statins in aortic valve disease, by Cowell et al. (39), found that high-dose atorvastatin did not slow the progression of aortic stenosis in this patient population. The SALTIRE (Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression) study initiated atorvastatin in patients who had more advanced aortic stenosis as defined by a mean aortic valve area of 1.03 $cm^2$, as compared with the mean aortic valve area in the RAAVE study of 1.23 $cm^2$ at baseline before treatment with rosuvastatin. The RAAVE study tested an open-label hypothesis approach to determine whether statin therapy for elevated LDL is beneficial earlier in the natural history of asymptomatic aortic stenosis. The RAAVE study did not measure calcium scores, so no comparison can be made in terms of this calcification marker. However, the SALTIRE study's initial patient population had elevated calcium scores present in the aortic valves, indicating a heavy burden of valve calcification (35,36,40) present in the initial study population, which again correlates with the more severe aortic valve area at baseline in the SALTIRE study as compared with the RAAVE study.

Rosenhek et al. (40) have previously shown that calcification is an important marker for the severity and outcomes of patients with aortic stenosis, therefore indicating that the large burden of calcification in the aortic valve predicts a higher risk for this patient population. We believe that the degree of aortic stenosis will be the most beneficial in the sclerotic or milder phase. We hypothesize that the treatment effect is probably caused by lipid and non–lipid-lowering effects of the statins, which have been described in a retrospective clinical report (15) and experimental studies. Recent experimental studies have shown that Lrp5, the LDL co-receptor, regulates calcification in the aortic valve and aorta (41,42). Rajamannan et al. (33) have shown in experimental animal models the potential non–lipid-lowering effects of statins in the aortic valve, including inhibition of an Lrp5-mediated cellular proliferation and activation of the osteogenic gene program in the aortic valve myofibroblast. The other well-known non–lipid-lowering effect of statins in the vasculature is the improvement in endothelial function via modulation of endothelial nitric oxide

synthase (43). Rajamannan et al. (32) have shown modulation of endothelial nitric oxide synthase enzymatic activity in the aortic valve of the experimental model of valve atherosclerosis. The SALTIRE trial was a landmark trial showing that patients with more a severe degree of aortic stenosis associated with a heavily calcified aortic valve would not respond to high-dose atorvastatin therapy. Finally, the RAAVE data also suggest that rosuvastatin has a lipid-lowering effect in slowing the progression in aortic valvular disease by targeting LDL in this patient population as compared with the SALTIRE trial.

This was a nonrandomized, prospective, open-label, observational study. Therefore, it should be considered only hypothesis generating. In this study, patients meeting NCEP-ATPIII guidelines are treated with statins. In future randomized blinded trials, the most important question to answer is whether those with lower cholesterol with no indication for statin therapy according to current guidelines would derive benefit from statins in terms of aortic stenosis progression and clinical events such as death or aortic valve replacement. These results will provide further supportive evidence for ongoing randomized clinical trials such as ASTRONOMER (Aortic Stenosis Progression Observation Measuring Effects of Rosuvastatin [Canada]), SEAS (Simvastatin and the Ezetimibe in Aortic Stenosis [Europe]) (44), and STOP-AS (Stop Aortic Stenosis [Cleveland Clinic, Cleveland, Ohio]) . The RAAVE study suggests that earlier treatment with statins is more efficacious in the prevention of progression of aortic valve stenosis than late treatment, similar to the effects of statins in the regression of vascular atherosclerosis (22).

Importantly, results of the randomized trials will provide further evidence to define the treatment of this complex disease process, in which timing of therapy and characteristics of the valve lesion will need to be taken into account in the future treatment approaches. In the RAAVE trial, the rate of progression of aortic stenosis in those with hypercholesterolemia treated with rosuvastatin is slower than in those with lower lipid levels who are not treated. This is the first study to provide positive clinical evidence for the potential of targeted therapy in patients with asymptomatic aortic stenosis.

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